Page 2	between lines 5 and 6,	please insert: --SUMMARY OF THE INVENTION--;
	in line 9,	please cancel: "of claim 1. The"; and
	in line 10,	please cancel "subclaims pertain to preferred embodiments of the method".
Page 8,	between lines 6 and 7,	please insert: --DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS--.

REMARKS

Reconsideration of this patent application is respectfully requested, in view of the foregoing amendments and the following remarks.

The amendments to this patent application are to revise the Specification in order to insert the various section headings which are required according to U.S. practice. Also a reference to the claims in the specification has been deleted.

The Applicants comment upon the formal objections to the claims 35 U.S.C. 112 as follows.

The present invention is directed to a diagnostic method. It provides a general method for identifying the condition (e.g. healthy or suffering from one or more diseases) of an organism. The method employs references not only to healthy organisms, but also includes several references from organisms suffering from different diseases. Having compiled sufficient references, the measurement of

peptides from a further organism in question provides information about the condition or status of the organism by comparison to these previously compiled references. It is part of the inventive method to collect these necessary references.

As an example, if reference measurements have revealed that a foreign disease X is affecting an organism, then disease X typically causes the concentration of peptide A and B to increase, while peptide C is lowered, and that a new peptide D will appear in comparison to healthy organisms. Then one would logically assume that a further organism showing also increases in peptides A and B, plus a lowering of peptide C, and having a new peptide D would also suffer from illness X. For the method of the present invention it is not necessary to know the sequence or the physiological role of peptides A, B, C, and D. This is what is meant by the terminology "without the need to recur to hypotheses". It is not necessary to create a hypotheses about the function or source of peptide D. This is in contrast to conventional methods wherein e.g. an infection with Hepatitis is identified by the analysis of the Hepatitis antigen or the analysis of proteins of the clotting cascade to identify the nature of a clotting disease.

The Patent Examiner raised objections under 35 U.S.C. 112. The terms "condition", "hypotheses" and "reference" have been explained above. The term "dipeptides" is used for peptides consisting of two aminoacids. Claim 4 describes a preferred embodiment wherein the measured peptides have a molecular weight which at least

corresponds to that of dipeptides i.e. is higher than that of the "dipeptide" having the lowest molecular weight which is gly-gly.

The term "derived" in claim 11 is not used to imply any special steps to collect a sample from the organism. It is clear to a person skilled in the art that some steps may be necessary to prepare a sample for measurement, especially depending on the method of measurement. Several methods for sample preparation have been given in the examples e.g. for the recovery from blood filtrate, ascetic fluid, and urine.

For all these reasons, all the claims are in complete compliance with the requirements of 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

The Applicants comment upon the prior art rejections of the claims as follows.

The Patent Examiner has cited *Ausubel*, "Short Protocols in Molecular Biology". The Office Action is correct that *Ausubel* discloses a number of methods for protein analysis. Although the claimed method of the present invention uses methods for the analysis of peptides it does not read on methods disclosed in *Ausubel*. For example, *Ausubel* discloses immunoaffinity chromatography. Immunoaffinity chromatography requires the use of antibodies bound to a matrix e.g. sepharose. Because the antibodies in the prior art are directed against a peptide or a protein, immunoaffinity chromatography can only purify special peptides for which antibodies are available. This requires at least a

hypotheses about which proteins or peptides can be found in the sample.

Furthermore, *Ausubel* discloses metal-chelate affinity chromatography. Metalchelate affinity chromatography requires the presence of a so-called His-Tag at the protein. Thus only special proteins can be analyzed through this method.

Ausubel further discloses reversed-phase HPLC, ion-exchange HPLC and size-exclusion HPLC. These methods differ from the claimed method of the present invention in that they are not used to detect the condition of an organism by relating the low-molecular weight peptides to references from other organisms. Furthermore, size-exclusion and ion-exchange HPLC do not permit any detection or characterization of low molecular weight peptides, as claimed

Harry et al disclose methods for the antigen detection of HIV. These antigens mainly are derived from the major HIV core protein p24, (See page 242, left column). Therefore, all assays are directed from the detection of this protein or fragments thereof. These methods are based on the hypotheses that the detected protein or fragment is relevant for the condition of an organism, e.g. whether or not the organism is infected with HIV. As it is explained above, the method of the present invention in contrast relies on the analysis of low molecular weight peptides without knowing their actual function.

Additionally, *Harry et al* relies on indirect assay methods, see for example page 241, right column, whereas the present

invention is directed to direct measurement methods. Also, *Harry* fails to teach the claimed low molecular weight peptide detection and characterization.

Jimenez et al discloses the measurement of neuropeptide expression and processing in the neurons of the mollusc *Lymnaea stagnalis*. Most of neuropeptides were known as can be derived from the introduction and especially figure 1, see further first two sentences of "Results and Discussion" on page 405. This is in contrast to the method of the present invention which is "without the need to recur to hypotheses". It is not necessary to know weight, concentration, or function of the peptides. Furthermore, *Jimenez et al* have not related the measurements to a reference from an organism or to references from different organisms in different conditions. *Jimenez* do not provide any conclusions about the condition of an organism.

Jiminez on page 404 in the right hand column discloses that matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS), pioneered by *Karas et al (1987)* and recently shown to be useful in the analysis of biological tissue (*van Veelan et al., 1993)*, can be used for direct mass analysis of intact peptides in single neurons. MALDI-MS can detect high-molecular-weight substances, is extremely sensitive, and can tolerate more impurities in the sample than other mass spectrometric methods.

Thus, *Jimenez* can only detect high-molecular weight substances, and does not detect the claimed low molecular weight

peptides, which are characterized and related to a reference.

Finally, none of the prior art references discloses the detection of qualitative and quantitative changes. This is an important improvement and advantage of the present invention, as discussed in the paragraph bridging pages 7 and 8 of the present Specification, as follows.

The data about patients with a known basic disease obtained from the above mentioned steps are compared to the similarly obtained data from a healthy reference population. Both qualitative changes (e.g., the occurrence of new peptides or the lacking of peptides) and quantitative changes (the increased or decreased occurrence of individual peptides) are detected. If required, the targets defined by the comparative analysis may further be purified and identified by methods of peptide chemistry known to those skilled in the art. The sequence information obtained can then be compared with protein and nucleic acid data bases and subsequently with data from the literature. The relevance of the represented peptides with respect to the examined disease is checked by functional studies and by screening with appropriate groups of patients.

For all of the above reasons, none of the prior art references provides an identical disclosure of the claimed invention. Hence, the present invention is not anticipated under 35 U.S.C. 102. Withdrawal of this ground of rejection is respectfully requested.

Also, none of the prior art references teaches or suggests the present invention and none of the prior art references provides a basis for any rejection under 35 U.S.C. 103. A prompt notification of allowability is respectfully requested.

Respectfully submitted,

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Encl.: Copy of Petition for Two Month Extension of Time for a Small Entity

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on JULY 31, 2000

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Ingrid Mittendorf